## REMARKS

### *I. Status Summary*

Claims 56-89 are pending in the present U.S. patent application and have been examined. An Official Action (hereinafter the "Official Action") was issued December 16, 2003 by the United States Patent and Trademark Office (hereinafter the "Patent Office").

Claims 56-89 have been rejected under 35 U.S.C. §101 upon the contention that the claimed invention is directed to non-statutory subject matter as the antibodies as claimed encompass naturally-occurring antibodies.

Claims 74-75, 80, and 89 have been rejected under 35 U.S.C. § 112, first paragraph, upon the contention that the specific cell lines recited in the claims must be known and readily available to the public in order to satisfy the enablement requirement. The Patent Office contends that the terms of the deposit of the cell lines are not clear from the specification.

Claims 56-89 have been rejected under 35 U.S.C. § 112, first paragraph, upon the contention that an improper incorporation by reference has been included in the specification relating to the sequence set forth in Ostman et al. (1994) Proc Natl Acad Sci U S A 91:9680-4 (hereinafter "Ostman").

Claims 56, 62, 68-69, 73, 76-77, and 82 have been rejected under 35 U.S.C. § 102(b) over Honda et al. (1994) Blood 81:4186-94 (hereinafter "Honda").

Claims 56-58, 60-62, 68-73, 76-79, and 81-82 have been rejected under 35 U.S.C. § 103(a) upon the contention that the claims are unpatentable over Honda in view of Tonks et al. (WO 95/30008; hereinafter "Tonks").

The specification has been amended to provide reference to SEQ ID NO: 4, which is the amino acid sequence of a DEP-1 polypeptide as reported by Ostman. Support for this amendment can be found throughout the specification as filed, including particularly at page 82, lines 13-15, and page 96, lines 19-22. Concurrently with this amendment to the specification, a Substitute Sequence Listing has been provided that includes SEQ ID NOs: 3 and 4, which correspond to the nucleic acid and amino acid sequences, respectively, of DEP-1 that are presented in Ostman and originally

incorporated by reference into the instant application. As the material added to the Substitute Sequence Listing includes only the material originally incorporated by reference, no new matter has been added.

Claim 62 has been canceled. Claims 56-61 and 63-89 have been amended. Support for the amendments can be found throughout the specification as filed, including particularly at page 45, lines 13-14. Additional support for the amendments can be found at page 82, line 13 (amino acids 175-536 of the ectodomain), at page 20, lines 4-7 (modulate angiogenesis), and at page 32, lines 8-10 (pharmaceutically acceptable in humans), the last element of which is also supported in light of the disclosure of treatment of human patients.

New claims 90-92 have been added. Support for the new claims can be found throughout the specification as filed, including particularly at page 19, line 23, through page 20, line 11, and at page 23, lines 19-20 ("modulating" encompasses "inhibiting"). No new matter has been added by any of the amendments to the specification or claims, or by the addition of the new claims. Reconsideration of the application as amended and based on the arguments set forth herein below is respectfully requested.

## *II. Rejection under 35 U.S.C. §101*

Claims 56-89 have been rejected under 35 U.S.C. §101 upon the contention that the claimed invention is directed to non-statutory subject matter. According to the Patent Office, claims 56-89, as written, do not sufficiently distinguish the claimed antibodies from naturally occurring antibodies. The Patent Office has suggested that the claims be amended to recite "isolated" or "purified" antibodies.

Applicants have amended claims 56-89 to recite that the claimed antibodies are isolated antibodies. Applicants would like to thank Examiner Yaen for his suggestion regarding addressing the instant rejection. Claim 62 has been canceled, and thus applicants believe that the rejection of this claim on this basis has been rendered moot. As a result, applicants respectfully request the withdrawal of the rejection of claims 56-61 and 63-89 under 35 U.S.C. § 101.

## *III. Rejections Based on 35 U.S.C. § 112, First Paragraph*

Claims 74-75, 80, and 89 have been rejected under 35 U.S.C. § 112, first paragraph, upon the contention that the claims fail to comply with the enablement requirement with regard to the deposit of hybridoma cell line HB12570 with the American Type Culture Collection (hereinafter "ATCC"). Additionally, claims 56-89 have been rejected under 35 U.S.C. § 112, first paragraph, upon the contention that the claims fail to comply with the enablement requirement regarding the incorporation by reference of the sequence of the DEP-1 cDNA and polypeptide as disclosed in Ostman. After careful consideration of the rejections and the Patent Office's bases therefor, applicants respectfully traverse the rejections and submit the following remarks.

### *III.1. Applicants' deposit of hybridoma cell line HB12570 satisfies the enablement requirement.*

The Patent Office asserts that claims 74-75, 80, and 89 fail to satisfy the enablement requirement of 35 U.S.C. § 112, first paragraph, because it is not clear that the cell line recited in the claims and therefore required to practice the claimed invention is known and/or readily available to the public or obtainable by a repeatable method set forth in the specification.

Applicants initially respectfully submit that it would appear that the application of the instant rejection to claim 80 is an error, as claim 80 does not recite an element related to a deposit of biological materials. Consequently, applicants respectfully request that the instant rejection of claim 80 be withdrawn.

Turning now to claims 74-75 and 89, applicants respectfully submit that the specification as filed clearly on page 42 that hybridoma cell line HB12570 was deposited with the American Type Culture Collection (ATCC) under the terms of the Budapest Treaty. Applicants further submit that ATCC is an International Depository Authority (IDA) under the International Budapest Treaty. Accordingly, applicants respectfully submit that the deposit of hybridoma cell line ATCC HB12570 complies with all requirements of the United States Patent and Trademark Office for the deposit of biological materials. Additionally, applicants' representative hereby submits a

Declaration Pursuant to 37 C.F.R. § 1.808, which specifically recites the terms under which the deposit was made. Applicants' representative respectfully submits that these terms are identical to those required by the Budapest Treaty.

Applicants further respectfully submit that the specification as filed complies with the requirements of 37 C.F.R. § 1.809. According to Rule 809, the specification must disclose the following:

(a) the accession number for the deposit;

(b) the date of the deposit;

(c) a description of the deposited biological material sufficient to specifically identify it and to permit examination; and

(d) the name and address of the depository.

Looking to the specification as filed, applicants respectfully submit that page 42 recites the following:

> Preferred monoclonal antibodies which preferentially bind to ECRTP/DEP-1 include a monoclonal antibody having the immunoreaction characteristics of Mab ECRTPAb-1, having molecular weight of about 150 KDa respectively and which binds to the ectodomain of the ECRTP/DEP-1, as is described herein below. Mab ECRTPAb-1 is preferably secreted by hybridoma cell line ATCC HB12570. The hybridoma cell line ATCC HB12570 was deposited pursuant to Budapest Treaty requirements with the American Type Culture Collection (ATCC), 10801 University Boulevard, Manassas, Virginia, 20110-2209, U.S.A., on September 18, 1998.

Furthermore, page 46 indicates that ATCC HB12570 is the hybridoma cell line that secretes monoclonal antibody ECRTPAb-1 as described in the Examples, and the Brief Description of Figure 12 presented on page 18 states that Figure 12 is an autoradiograph showing that ECRTPAb-1 binds peptide sequence QSRDTEVL of the ECRTP/DEP-1 ectodomain.

As such, applicants respectfully submit that the specification as filed clearly states that a hybridoma cell line with accession number HB12570, which is a hybridoma cell line that produces monoclonal antibody ECRTPAb-1 that binds to the peptide sequence QSRDTEVL of the ECRTP/DEP-1 ectodomain, was deposited on September

18, 1998 with the American Type Culture Collection at 10801 University Boulevard, Manassas, Virginia, 20110-2209, U.S.A., under the terms of the Budapest Treaty.

Accordingly, applicants respectfully submit that they have made a deposit of hybridoma cell line HB12570 with ATCC under terms that satisfy the Patent Office's Deposit requirements as listed in 37 C.F.R. 1.803-1.809. Applicants further respectfully submit that this deposit satisfies the enablement requirement of 35 U.S.C. § 112, first paragraph. Thus, applicants respectfully request the withdrawal of the rejection of claims 74-75, 80, and 89 on this basis.

*III.2. Applicants' amendments to the specification address the asserted improper incorporation by reference.*

Claims 56-89 have been rejected under 35 U.S.C. § 112, first paragraph, upon the contention that an improper incorporation by reference has been included in the specification relating to the sequence set forth in Ostman.

To address this rejection, applicants have amended the specification at pages 82 and 96 to include reference to SEQ ID NOs: 3 and 4, which correspond to the nucleic acid and amino acid sequences, respectively, of DEP-1 that are presented in Ostman. Additionally, applicants submit the following:

1. A Substitute Sequence Listing that includes SEQ ID NOs: 3 and 4, along with all required documentation related to the submission of a Substitute Sequence Listing.
2. A Hawkins Declaration to accompany amending the instant specification to provide the asserted essential material incorporated by reference set forth in Ostman.

As a consequence of the amendments to the specification and the additional material submitted, applicants respectfully submit that the rejection of claims 56-89 under 35 U.S.C. § 112, first paragraph, has been addressed. Claim 62 has been canceled, and thus the rejection of this claim on this basis is believed to have been rendered moot. Accordingly, applicants respectfully request the withdrawal of the rejection of claims 56-61 and 63-89 on this basis.

*IV. Rejection Based on 35 U.S.C. § 102*

Claims 56, 62, 68-69, 73, 76-77, and 82 have been rejected under 35 U.S.C. § 102(b) over Honda. According to the Patent Office, Honda discloses an antibody that is generated from a peptide fragment within amino acids 175-536, which corresponds to amino acids 293-536. Furthermore, the Patent Office asserts that since the antibody was derived from rabbit serum, it is already in a pharmaceutically acceptable carrier. And finally, the Patent Office contends that the recited functional limitation of having angiogenesis modulating activity would be an inherent property of the antibody taught by Honda. After careful consideration of the rejection and the Patent Office's bases therefor, applicants respectfully traverse the rejection.

Initially, applicants respectfully submit that it appears that the epitope used by Honda corresponded to amino acids 263-505 of DEP-1, and not to amino acids 293-536. This point is mentioned for clarification.

Claims 56, 68, 76, and 82 have been amended to recite an isolated antibody in a diluent or excipient pharmaceutically acceptable in humans. Support for the amendment can be found throughout the specification as filed, including inter alia, at page 25, lines 13-24, and at page 32, lines 4-10, which disclose administration of the therapeutic composition in an appropriate carrier to a human patient. Additional support can be found at page 32, line 3, through page 34, line 11, which disclose therapeutic compositions and pharmaceutically acceptable carriers.

Applicants respectfully submit that Honda discloses a polyclonal rabbit antiserum, which the Patent Office asserts constitutes an antibody "already in a pharmaceutically acceptable carrier". Official Action at page 9. With regard to the Patent Office's assertion that rabbit serum is a pharmaceutically acceptable carrier, applicants respectfully submit that rabbit serum is not a pharmaceutically acceptable carrier for use in humans.

Accordingly, applicants respectfully submit that Honda does not disclose each and every limitation of the claims, and thus does not anticipate claims 56, 68, 76, and 82, which include this element. Claims 62, 69, 73, and 77 all depend directly from claim 56, 68, or 76, and thus include this distinguishing element. Claim 62 has been

canceled, and thus the rejection of this claim is believed to have been rendered moot. Accordingly, applicants respectfully request the withdrawal of the rejection of claims 56, 68-69, 73, 76-77, and 82 on this basis.

## *V. Rejection Based on 35 U.S.C. § 103(a)*

Claims 56-58, 60-62, 68-73, 76-79, and 81-82 have been rejected under 35 U.S.C. § 103(a) upon the contention that the claims are unpatentable over Honda in view of Tonks. After careful consideration of the rejection and the Patent Office's bases therefor, applicants respectfully submit that the Patent Office has not met its burden in establishing a prima facie case of obviousness.

### *V.1. The cited combination does not disclose each and every element of the claims at issue.*

In order to support a prima facie case of obviousness under § 103, the cited references must disclose or suggest all the claim elements. Applicants respectfully submit that the combination of Honda and Tonks fails to disclose or suggest all the elements of the currently claimed subject matter. Particularly, the cited combination does not teach or suggest an antibody in a diluent or excipient pharmaceutically acceptable in humans. Each of the instantly rejected claims recites this element directly or indirectly. As discussed in more detail hereinabove, Honda does not disclose antibodies provided in such a diluent or excipient. Neither does Tonks disclose such an element. Since the cited combination of references does not disclose each and every element in the claimed subject matter, applicants respectfully submit that a rejection under § 103 cannot be properly made. See MPEP § 2143.03.

### *V.2. There is no motivation seen in the cited references to modify the combined disclosure to arrive at the presently claimed subject matter.*

In order to establish a prima facie case of obvious, the cited document or combination must also contain a suggestion to modify the cited document(s) to arrive at the presently claimed subject matter. Applicants respectfully submit that the

combination of Honda and Tonks does not contain any suggestion or provide any motivation to place anti-DEP-1 antibodies in a diluent or excipient pharmaceutically acceptable in humans.

In attempting to establish a motivation in the cited combination in the present rejection of record, the Patent Office asserts that one of ordinary skill in the art would have been motivated to produce "DEP-1 monoclonal antibodies, fragments of DEP-1 antibodies... and humanized forms of DEP-1 antibodies... because DEP-1 had been found to be a PTPase that may be important in signal transduction, and that Tonks *et al* disclosed that modulation of such PTPase activity can be accomplished by using antibodies to the DEP-1 wherein the antibodies could be in the form of monoclonal, fragments, and chimeric antibodies." Official Action at page 10. Applicants respectfully submit that the Patent Office is taking disparate elements of Tonks out of context in order to generate the asserted motivation, and that when the disclosure is viewed in its entirety, the overall teaching is clearly to the contrary. As such, Tonks does not support the deficiencies of Honda with regard to providing a motivation, in that the antibodies disclosed in Honda were used in Western blotting experiments.

To elaborate, Tonks discloses that protein tyrosine phosphatases (PTPs) as a class are interesting molecules that have been implicated in a large range of activities that might have intriguing biological roles. For example, page 6 of Tonks recites the following:

> These observations lead to speculation regarding PTP involvement in modulation of cytoskeletal integrity, as well as other related cellular phenomena such as transformation, tumor invasion, metastasis, cell adhesion, and leukocyte movement along and passage through the endothelial cell layer in inflammation.

As such, applicants respectfully submit that Tonks discloses no more than that there has been conjecture regarding the class of PTPs in a wide range of biological functions, and thus are candidates for further experimentation into their roles in these functions.

Applicants respectfully submit that when the above passage is taken in context, this extensive list of potential activities of PTPs does not provide a motivation to produce the claimed antibodies in a diluent or excipient pharmaceutically acceptable in

humans. Rather, it is clear that Tonks provides only a discussion of PTPs generally, and further that these thoughts amount to no more that a disclosure of an interesting branch of research into general mechanisms of potential interest. As such, applicants respectfully submit that at most, this sort of speculation is an invitation to explore a branch of research involving the members of various PTPase families.

Thus, there is no reasonable motivation or incentive seen in the cited combination for one to make the presently claimed subject matter unless there is an intention to use the antibody as a pharmaceutical that is acceptable in humans. Likewise, neither can either of the references provide motivation to administer the claimed composition absent a reasonable expectation of a useful therapeutic outcome. Speculation concerning a laundry list of possible biological roles of DEP-1 is not adequate incentive to make the claimed subject matter. Nothing can be found in Honda to remedy these deficiencies in Tonks.

Applicants further respectfully submit that the only motivation to prepare an antibody against DEP-1 in a pharmaceutical carrier suitable for use in humans can be found in the specification of the instant application, and thus a rejection under 35 U.S.C. Section 103 based on the combination of Tonks and Honda represents an impermissible hindsight reconstruction by the Patent Office. The combination of references provides at best an "ought to be tried" scenario. Applicants respectfully submit that a rejection based on either premise, as is the instant rejection, has been clearly proscribed by the Court of Appeals for the Federal Circuit in Hodosh v. Block Drug Co. (786 F.2d 1136, Fed. Cir. 1986), which held that references must be reviewed without benefit of hindsight vision afforded by the claimed subject matter (*see also* MPEP § 2142) and that "ought to be tried" is not the standard with which obviousness is determined. Thus, applicants respectfully submit that the cited combination of Honda and Tonks does not suffice to establish a prima facie case of obviousness.

*V.3. Summary*

In conclusion, the cited combination of Honda and Tonks does not support a prima facie case of obviousness because the cited references do not disclose each and

every element of the claims and because the cited references do not contain a suggestion to modify the cited document(s) to arrive at the claimed subject matter. Accordingly, applicants respectfully submit that a prima facie case under 35 U.S.C. § 103(a) has not been presented regarding claims 56-58, 60-62, 68-73, 76-79, and 81-82 over Honda in view of Tonks. Claim 62 has been canceled, and thus the rejection of claim 62 on this basis has been rendered moot. Applicants respectfully request the withdrawal of the rejection under 35 U.S.C. § 103(a) of claims 56-58, 60-61, 68-73, 76-79, and 81-82 over Honda in view of Tonks. Allowance of these claims is also respectfully requested.

## *VI. New Claims*

New claims 90-92 have been added. These claims recite the antibodies, fragments, and derivatives thereof of claims 68, 76, and 83, respectively, wherein the activity in modulating angiogenesis is inhibition of angiogenesis. Support for the new claims can be found throughout the specification as filed, including *inter alia* at page 19, line 23, through page 20, line 11 (antibodies as angiogenesis inhibitors), and at page 23, lines 19-20 ("modulating" encompasses "inhibiting"). Applicants respectfully submit that the new claims are in condition for allowance, and respectfully solicit a Notice of Allowance to that effect.

## *VII. Allowable Subject Matter*

Applicants note that the Patent Office has indicated that claims 61, 63-67, 74-75, and 83-89 appear to be free of the prior art. Applicants respectfully submit that no art has been cited against claim 59 or claim 80, and thus applicants believe that these claims are also free of the prior art. However, claim 61 has been rejected under 35 U.S.C. § 103(a). Applicants believe that the inclusion of claim 61 in this rejection was unintended, and thus believe that claims 59, 61, 63-67, 74-75, 80, and 83-89 are free of the prior art. In view of the amendments and remarks presented herein, applicants respectfully submit that the non-prior art rejections of these claims have been addressed.

## CONCLUSIONS

In light of the above Amendments and the Remarks presented hereinabove, it is respectfully submitted that claims 56-61 and 63-89 are in proper condition for allowance, and such action is earnestly solicited.

If any minor issues should remain outstanding after the Examiner has had an opportunity to study the Amendment and Remarks, it is respectfully requested that the Examiner telephone the undersigned attorney so that all such matters may be resolved and the application placed in condition for allowance without the necessity for another Action and/or Amendment.

## DEPOSIT ACCOUNT

The Commissioner is hereby authorized to charge any deficiencies or credit any overpayments associated with the filing of this correspondence to Deposit Account Number **50-0426**.

Respectfully submitted,
JENKINS, WILSON & TAYLOR, P.A.

Date: April 15, 2004 By: _____
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